to induce molecular remissions in a proportion of patients, which in turn has translated to improved progression-free and overall survival. Their results underscore the importance of designing prospective trials to better define the role of allogeneic transplant in myeloma, specifically the patient population that might benefit and the conditioning approach that is most appropriate.

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Hyperferritinemia in Stem Cell Transplantation

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Since the initial study of Altes and colleagues in 2002 [1], a large number of publications have reported a strong association between elevated serum ferritin before allogeneic hematopoietic stem cell transplantation (HSCT) and decreased post-HSCT overall survival (OS). Although this association is now beyond doubt, many areas of uncertainty remain.

In this context, the study of Dr. Meyer and colleagues [2] in this issue of *Biology of Blood and Marrow Transplantation* adds both light and darkness. They report the dynamic behavior of serum iron parameters, most notably ferritin, among 290 patients who underwent myeloablative HSCT at their center. As previously described, ferritin levels increased in the few months after transplantation and then decreased to below pre-HSCT levels in long-term survivors. They also could confirm that pre-HSCT ferritin is associated with increased nonrelapse mortality (NRM) and decreased OS. However, the most important finding of this study is that an elevated ferritin was associated with increased mortality even in 6-, 12-, and 24-month landmark analyses. This effect appeared to depend on both an increased risk of relapse and an increased risk of NRM in patients with elevated ferritin. This finding can be interpreted in at least three different ways.

First, it is possible that iron overload is indeed detrimental after HSCT, as previously assumed based on ferritin studies and for the reasons previously adduced: increased risk of infection, especially fungal, and liver toxicity. The present study would suggest that this effect extends to long-term survivors of HSCT. However, this seems the least likely explanation. Indeed, long-term mortality after HSCT depends primarily on disease relapse and complications of chronic graft-versus-host disease (GVHD), not liver toxicity (which is a very rare cause of death after the early post-HSCT period) or fungal infection (outside of the context of chronic GVHD and immunosuppression). There has been little evidence to date that hyperferritinemia is associated with the subsequent development of chronic GVHD. In Dr. Meyer's study, the adverse effect of hyperferritinemia on long-term survivors was primarily due to relapse, not NRM, which is

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clearly the opposite of its effect early after HSCT (which, based on nearly all published studies on the topic, including the present one, is driven primarily by an increase in NRM).

The second interpretation would be that iron overload exerts influences that are not limited to those commonly suspected and that its effect is modulated by the clinical context. Early after HSCT, with the myeloablative conditioning-induced rise in labile plasma iron, the major toxicities would relate to infection and liver toxicity, which may depend more on labile than parenchymal iron. Late after HSCT, when iron overload may be associated with less labile iron elevation, iron overload could modulate antitumor immunity or directly impact tumor growth. Indeed, there are now anecdotal reports that iron chelation may be associated with antitumor activity, consistent with an interaction between iron homeostasis and tumor growth.

Third, it may be that the effect of hyperferritinemia has little to do with iron overload. Despite the widespread assumption that our knowledge of hyperferritinemia can be directly translated to iron overload (witness the first sentence of Dr. Meyer's abstract), this fact has not yet been proven. Ferritin is undeniably strongly correlated with iron burden, with a correlation coefficient between it and liver iron content reported to be around 0.6 to 0.75. This means, however, that one half to two thirds of the variance in ferritin values depends on factors other than iron burden, including inflammatory issues, which we know to be prognostically relevant in HSCT [3].

Three recent HSCT studies have examined the prognostic importance of iron overload as determined by magnetic resonance imaging–quantified liver iron content, which presumably is a better reflection of iron burden than ferritin. Two of the studies found no association of liver iron content with NRM or OS, whereas one did [4-6]. Therefore, at this time the question remains: is iron overload truly associated with increased post-HSCT mortality? And if not, what does hyperferritinemia mean?

The most pedestrian explanation of much of the ferritin literature is that it simply reflects ferritin's role as a marker of acute phase/inflammatory issues, caused by tumor, organ toxicity, and GVHD, which are all going to be strongly tied to HSCT outcome. Our ability to adjust for this, by including in the multivariable models other acute phase reactants, markers of disease risk such as the European Group for Blood and Marrow Transplantation risk score, or covariates for the occurrence of GVHD (as done by Dr. Meyer and colleagues), is commendable but limited because we do not have very good tools to account for organ injury, infection, disease relapse risk, or GVHD severity. The possibility of confounding by any of these remains strong.

How will we resolve this question? At this point, we likely have drawn dry the well of ferritin-based knowledge. We now need more and larger studies that incorporate direct measurements of parenchymal and labile iron. Only through those will we be able to provide definitive answers regarding the role of iron overload in HSCT. In the words of Tennyson, it may be that the gulfs will wash us down, and that we will find very little effect of iron overload in HSCT and put the iron issue to rest. Or it may be that we shall touch the Happy Isles and learn about simple and complex ways through which iron overload impacts transplant toxicity and tumor growth. Then, and perhaps only then, can we take the next challenge: to learn how to use chelation strategies pre- and post-HSCT to mitigate those risks and make HSCT safer and more effective.

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